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EXAMINER	
MYERS, CARLA J	

ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/081,955	SEIDEL ET AL.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 September 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *124-141* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *124-141* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *11-20-06* .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in reply to the response filed September 13, 2006. Applicant's arguments have been fully considered but are not persuasive to overcome all grounds of rejection. This action is made final.

Claims 124-141 are pending and have been examined herein.

Maintained Rejections

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 124-141 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to done skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The specification as originally filed does not appear to provide support for the claimed methods of producing multiple embryos from a female bovine comprising the steps of superovulating a female bovine, establishing an insemination sample having half the number of sperm of a typical unsorted insemination sample, inserting the insemination sample into the uterus of a female bovine and fertilizing a plurality of eggs "at success levels selected from the group consisting of at least 35%, at least 41%, at least 50%, and at least 90% of a typical unsorted insemination dosage."

The specification (page 19) states that artificial insemination with 100,000 and 250,000 sperm achieved 41% and 50% pregnancy rates. However, these teachings relate to the pregnancy rates obtained using sorted sperm. These rates do not pertain to pregnancy rates obtained in bovine that are superovulated or bovine that are inseminated with unsorted sperm. Further, the pregnancy rates are absolute numbers, as opposed to the % pregnancy rates compared to a typical unsorted insemination sample. The specification (page 19) cites Seidel (1997) as providing the details of the method in which the 41% and 50% pregnancy rates were obtained. In this paper, Seidel teaches that control bovine inseminated with a typical dosage (2.5×10^6) of sperm achieved pregnancy rates of 62% for ipsilateral insemination and 50% for contralateral insemination. Thereby, disregarding the fact that the method utilizes sorted sperm and that the bovine were not superovulated, the methods using $1/10^{th}$ of the typical insemination sample achieved pregnancy rates that were 80.6% that of a typical insemination dosage. Accordingly, these teachings do not provide support for the presently claimed invention which requires the use of superovulated bovine, the use of unsorted sperm, the use of less than one half the typical unsorted insemination sample, and a comparison of the fertilization rate to that obtained with a typical dosage of unsorted sperm. Also, the teachings regarding success rates of 41% and 50% do not provide basis for the concept of fertilization rates of 35%, 42%, 43%, 52% , 53% etc as encompassed by the claims.

In Example 1 (page 25), the specification provides the results of a method in which a $3 X10^5$ dosage of sorted sperm was used to inseminate cows that were not

superovulated and in which pregnancy rates of 80% of the controls were obtained. Example 2 (page 26) discloses a method in which bovine that were not superovulated were inseminated with 5 x 10^5 total sperm and pregnancy rates obtained "were similar" to those obtained with 10 x10^6 sperm. In example 3 (pages 26-27), 1 to 2 X10^5 of sex sorted sperm were used for the insemination of heifers that were not superovulated. None of the females became pregnant when inseminated with sperm shipped at ambient temperature, while 14/29 heifers became pregnant when inseminated with sperm cooled to 5°C during shipping. A comparison of fertilization rates to a typical dosage of unsorted sperm is not provided in this example. In example 4 (pages 27-28), single ovulatory heifers were inseminated with 1 or 2.5 X10^5 of sperm cooled to 5°C. Pregnancy rates were 41%, 52% and 56% for 1 X10^5 , 2.5 X10^5 and 2.5 X10^6 sperm/inseminate. Thereby, insemination rates were 93% of that of a typical dosage of sperm when 1/10^{th} the typical dosage of sperm was used for insemination. Each of the examples set forth in the specification utilized single ovulating bovine. No examples are provided in which the results obtained with superovulating bovine inseminated with one half the typical dosage of sperm are compared to superovulating or single ovulating cow inseminated with a typical dosage of sperm. There is also no clear disclosure in the specification of the specific results that one would expect to achieve when using one half the dosage of a typical unsorted insemination sample to inseminate superovulated bovine. Accordingly, the specification as originally filed does not appear to provide basis for the concept of a method in which unsorted or sorted sperm at one half of the typical unsorted insemination dosage or less are utilized to achieve fertilization rates in

superovulating bovine of at least 35% (36%, 37% etc), at least 41% (42%, 43% etc), at least 50% (51%, 52% etc) or 90% (91% , 92%...to 100%) of the typical unsorted insemination sample.

3. Claims 124-141 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of producing bovine offspring wherein the methods comprise collecting semen from a bovine, staining the sperm cells in the semen, sorting the sperm by sex chromosomes using a MoFlo flow cytometer / cell sorter at 50 psi using 2.9% Na Citrate as a sheath fluid, collecting the sperm at approximately 500 live sperm/second into tubes containing Cornell Universal Extender (CEU) with 20% egg yolk, and using, within 5-9 hours post-sorting, 3×10^5 live, cooled sperm to inseminate bovine that were previously synchronized with prostaglandin F-2 alpha at 12 day intervals, wherein said method results in pregnancy rates of about 80% of controls inseminated using 15.6×10^6 motile non-sorted/unsexed sperm (see page 25 of the specification), does not reasonably provide enablement for methods of producing multiple embryos from a bovine mammal comprising superovulating the bovine mammal to produce at least two eggs, inserting a portion of an insemination sample having a number of sperm cells at least half that of a typical unsorted insemination sample, fertilizing the eggs at success rates of at least 35%, 41%, 50% or 90% of that of a typical unsorted insemination dosage, and producing at least two embryos from said female bovine mammal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands,* 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Breadth of the Claims:

The claims are drawn to methods of producing multiple embryos from a bovine mammal comprising superovulating the bovine mammal to produce at least two eggs, inserting a portion of an insemination sample having a number of sperm cells at least half that of a typical unsorted insemination sample, fertilizing the eggs at success rates of at least 35%, 41%, 50% or 90% of that of a typical unsorted insemination dosage, and producing at least two embryos from said female bovine mammal. The claims further include staining the sperm and sorting the sperm according to a sex characteristic at sorting rates of 500 and 2000 sorts per second.

Nature of the Invention:

The claims encompass methods of sex sorting sperm and artificially inseminating superovulated bovine. The invention is in a class of inventions which the CAFC has characterized as 'the unpredictable arts such as chemistry and biology" (Mycolgen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Federal Circuit 2001)).

Teachings in the Specification and State of the Art:

The claims require superovulating a female bovine mammal and inseminating the superovulated bovine with one half the typical dosage of unsorted sperm. The specification (page 19) states that a typical dosage of sperm used for bovine insemination is about 1 to 10 million sperm. Accordingly, "one half of a typical unsorted dosage of sperm cells" has been interpreted as including 500,000 to 5 million sperm/insemination. The specification (page 19) teaches that insemination levels of 41% and 50% were achieved in single ovulating bovine inseminated with 100,000 and 250,000 sperm, respectively. It is stated (page 19) that "Since sperm cells appear to display a sensitivity to dilution, these results may display particular interdependence on the utilization of low dose sperm samples with regards to various techniques of the present invention."

At page 22, it is stated that "the techniques can be combined to achieve higher efficiency production as well. Particularly, the processes now invented which permit high speed sorting and low dose insemination of sexed embryos is also possible in a superovulated animal....the combination with superovulation is surprising because superovulation was previously deemed to hinder such a combination. Sperm transport is compromised in superovulated cattle, so animals were frequently artificially inseminated on multiple occasions and/or with multiple doses of semen. Also, prior procedures for sexing semen were relatively slow; therefore, it was of interest to determine fertilization rates after a single insemination of superovulatory pharmaceutical, such as FSH (follicle stimulating hormone)–treated cattle with only 600,000 total sexed unfrozen sperm using these newer combination of techniques. "

Thereby, the specification states in general that superovulated bovine can be inseminated with sex sorted sperm obtained using the high speed sorting techniques and using the sperm handling techniques set forth in the present application.

However, the specification does not provide any clear examples in which superovulated bovine are inseminated with sorted or unsorted sperm using one half of the typical unsorted insemination dosage of sperm cells and in which fertilization success rates of at least 35% to at least 90%, including 100%, of a typical unsorted insemination dosage are achieved.

The prior art of Brink (Theriogenology. 1994. 41: 168; cited in the Office action of 9/30/04; co-authored by one of the present inventors) teaches a method in which superovulated heifers are inseminated with "1 straw of semen." It is stated that embryos were collected from 82% of the cows. This reference does not teach the insemination dosage and does not teach the rate of fertilization, particularly the rate of fertilization as compared to a typical unsorted insemination dosage.

In each of the examples provided in the specification, single ovulating bovine were analyzed. In particular, example 1 (page 25) describes a method of using a "low dose" of sex sorted sperm for artificial insemination of a bovine. The method requires collecting a sperm sample from a bovine, staining the sperm cells in the semen, sorting the sperm by sex chromosomes using a MoFlo flow cytometer / cell sorter at 50 psi using 2.9% Na Citrate as a sheath fluid, collecting the sperm at approximately 500 live sperm/second into tubes containing Cornell Universal Extender (CEU) with 20% egg yolk, cooling the sperm sample, and using 3×10^5 live, cooled sperm to inseminate

bovine that were previously synchronized with prostaglandin F-2 alpha at 12 day intervals. The sorted sperm were used for insemination within 5-9 hours after sorting and the method resulted in pregnancy rates of about 80% of controls inseminated using 15.6 X 10^6 motile non-sorted/unsexed sperm. Example 2 (page 26) discloses a method in which bovine that were not superovulated were inseminated with 5 x 10^5 total sperm and pregnancy rates obtained "were similar" to those obtained with 10 x10^6 sperm. In example 3 (pages 26-27), 1 to 2 X10^5 of sex sorted sperm were used for the insemination of heifers that were not superovulated. None of the females became pregnant when inseminated with sperm shipped at ambient temperature, while 14/29 heifers became pregnant when inseminated with sperm cooled to 5°C during shipping. In one instance insemination with 1-2 X10^5 sperm in 0.1 ml resulted in pregnancy rates of 41% at 8 weeks and in pregnancy rates of 50% at 8 weeks when insemination was performed within 10 hours of the end of sorting. A comparison of fertilization rates to a typical dosage of unsorted sperm is not provided in this example. In example 4 (pages 27-28), single ovulatory heifers were inseminated with 1 or 2.5 X10^5 of sperm cooled to 5°C. Pregnancy rates were 41%, 52% and 56% for 1 X10^5 , 2.5 X10^5 and 2.5 X10^6 sperm/inseminate. Thereby, insemination rates with respect to a typical dosage of unsorted sperm were 93% when 1/10^{th} the typical dosage of sperm was used for insemination. Again, each of the examples set forth in the specification utilized single ovulatory bovine.

As noted in the response of September 13, 2006, at pages 22-23, the specification teaches a method in which 12 heifers were superovulated using 6, 6, 4, 4,

2, 2, 2, and 2 mg FSH beginning at days 9 and 12 of the estrous cycle and in which 25 and 125 mg prostaglandin F-2 alpha was injected following the 6^{th} and 7^{th} FSH injections. The superovulated heifers were inseminated using sperm sorted by staining with Hoechst 33342 following by sorting using a MoFlo flow cytometer using a sort rate of 800 liver sperm/sec. The total quantity of sperm used for insemination appears to be 6.18×10^5 cooled (unfrozen) sperm. The fertilization success rates are not clearly set forth in the example. Embryos were harvested from 9 of the 12 heifer, but the example does not indicate whether ova from the 3 remaining heifer were successfully fertilized. The example states that 52 of 96 (54%) ova produced embryos at normal stages of development or that 65 of 96 (68%) ova were fertilized. However, this disclosure does not clearly state the fertilization success levels achieved relative to a typical unsorted insemination sample.

The Predictability or Unpredictability of the Art and Degree of Experimentation:

The specification sets forth the unpredictability in the art of using superovulated bovine for artificial insemination purposes. The teachings in the prior art support this unpredictability. For instance, Donaldson (1985; cited in the IDS) teaches that insemination of superovulated bovine with "one unit" of semen," but does not specify the quantity of semen in each dosage. The reference teaches that using double units of semen or multiple units of semen at timed intervals does not improve the fertilization frequency (page 36). Donaldson (abstract) concludes that "one insemination of a donor cow 12 hours after the onset of oestrus with a single unit of semen is a satisfactory insemination regimen for the superovulation of cows. It is noted that the present claims

do not specify the time of insemination following the onset of estrus or the number of times the cow is inseminated. Further, the specification does not provide specific guidance as to how these parameters effect the fertilization rate in superovulated bovine inseminated with one half of the typical dosage of unsorted sperm. Seidel (1978. Control of Reproduction in the Cow, JR Sreenan ed., pages 268-280) teaches insemination superovulated bovine with dosages of 50 million unfrozen sperm or 60 million frozen sperm (see page 274). Seidel (page 277) reports that the previous history of the donor cows may be related to the recovery of normal of ova and thereby to the fertilization rate. Seidel (-age 277) also teaches that "significantly ($p < .05$) more normal ova were recovered from donors inseminated with unfrozen than with frozen semen. Thereby, the use of unfrozen versus frozen semen appears to be another factor which will effect the ability to use dosages of sperm of one half the typical insemination sample to inseminated superovulated bovine. Hawk (Journal Animal Sciences. 1986. 63: 551-560) teaches insemination of superovulated bovine with dosages of a total of 40 million sperm. Hawk (see abstract) teaches that the "(f)ertilization rate in first-service cows was 81% on the side of semen deposition and 68% on the opposite side ($P < .01$); the rates in repeat-breeders were 54% and 32% ($P < .0225$)." Thereby, Hawk teaches that factors such as whether the cow was previously bred and the side of insemination effect the frequency of fertilization. However, there are no specific teachings in the specification as to whether the use of repeat-breeder cows or site of insemination will effect the fertilization frequency of superovulated bovine inseminated with dosages that are one half that of the typical unsorted insemination dosage.

The specification also sets forth the unpredictability in the art of using sex sorted sperm for artificial insemination and particularly the unpredictability of using low-dosages of sex sorted sperm for AI. There are an extensive number of variables which effect the viability of the sperm, the success rate of AI, the ability to fertilize multiple eggs, and the pregnancy success rate.

For example, at page 3, the specification states that "the sperm are time-critical cells. They lose their effectiveness the longer they remain unused." In Example 3, the specification teaches that when 38 heifers were inseminated about 22 hours post-sorting, none of the heifers were pregnant 8 weeks after insemination. When inseminations were done 18-29 hours post-sorting, of 33 heifers only 1 remained pregnant at 8 weeks. Additionally, when inseminations were performed 17 to 24 hours post-sorting, only 1 of 7 inseminated females was pregnant at 8 weeks. The specification also emphasizes the unpredictability of using low dosage sex sorted sperm for insemination. However, the specification exemplifies using low dosages of sex sorted sperm only with bovine animals wherein the dosage is a minimum of 1-3 x 10^5 live, cooled sperm used within 10 hours of sorting. Given the unpredictability in using low dosages of sex sorted sperm for insemination purposes, it is highly unpredictable as to the quantity of bovine sperm that would acceptable to allow for fertilization success rates of at least 35%, 41%, 50%, 90%, or 100% comparable to those obtained with a typical unsorted insemination sample.

The specification (at page 27) also teaches that the handling of the sample post-sorting significantly effects the success of the insemination process. When insemination

samples were shipped at ambient temperature, 0 out of 10 females became pregnant. Only when the sperm was cooled to 5°C during shipping, was insemination effective.

At page 3-4, the specification discusses additional factors which hinder the use of sex-sorted sperm. It is stated that "the process through normal flow cytometer techniques may, in fact, be unacceptable for cytometric sorting of sperm cells in certain applications. The sensitivities range from dilution problems and the flow cytometers inherent need to isolate and distinguish each cell individually as well as the pressure sand other stresses which typical flow cytometry has, prior to the present invention imposed upon the cells or other substances that it was sorting. This may also represent a unique factor for sperm cells because it appears that even though the sperm cell may appear to pass through the flow cytometer and be sorted with no visually discernable side-effects, in fact, the cells themselves may have been stressed to the point that they perform less optimally in the insemination process." While this passage appears to state that these problems occurred only prior to the present invention, the specification and claims do not recite any particular advancements which allow for the ordinary artisan to overcome each of these problems when sorting sex from any organism, using any means for sensing a sex characteristic, any means for separating the sperm, any means for collecting the sperm, any means for storing and transporting the sperm, any low dosage of sperm and any means of artificial insemination. The specification teaches that the sorting rate and pressure used to run the flow cytometer may significantly effect sperm viability. However, the majority of the claims allow for the use of any type of apparatus to sense the sex characteristic and to separate the sperm cells based on the

sex characteristic. The specification does not provide sufficient guidance to enable the skilled artisan to use any apparatus under any conditions, and particularly under any conditions of pressure or sort rate, to generate insemination samples that achieve fertilization rates comparable to those obtained with unsexed, unsorted sperm cells.

The specification further teaches that the selection of a sheath fluid greatly influences the viability of the sperm cells. For instance, at page 12, the specification teaches that "the stress imposed by handling of the cells within the flow cytometer appears significant for this application...For instance, while it has been known to utilize fluids having a proper pH factor or osmoality, the present invention recognizes that there may be certain chemical compositions to which the cells may be hyper-responsive. These hyper-responsive chemical compositions may naturally vary based upon the cells or even the prior handling of the cells." The specification goes on to teach a specific citrate-based sheath fluid for sorting bovine cells. However, the specification does not teach other chemical compositions that are suitable for sorting bovine sperm. As set forth in the specification, a sperm cells response to a chemical will vary depending on the type of chemical, source of sperm cell and previous handling of the sperm cells. The identity of the chemicals that cause stress to sperm cells from other bovine, equine and other mammals can only be determined through experimentation. There is no predictable means for determining a priori which sheath fluids will impose minimal stress on the sperm cells and allow for the sorting of sperm cells to generate an insemination sample that can be used to fertilize eggs at success levels of up to 100% that of a typical unsorted insemination sample. In particular, with respect to claims 140

and 141, the specification has not enabled using any HEPES sheath fluid for the sorting of bovine sperm. The specification has stated that it is unexpected that HEPES-based HBGM3 solution was effective as a sheath fluid during the sorting of equine sperm. The specification has not taught that this solution can be used with other sperm cells or that other HEPES solutions can be used with bovine sperm cells. In view of the unpredictable effects that chemical compositions may have on the viability of sperm cells, undue experimentation would be required to practice the methods of claims 140 and 141as they are broadly claimed.

Other factors which influence sperm viability include different aspects of the collection process. At page 15, the specification teaches that "it may be important that the container which makes up the collector be properly sized so that it acts as some means of avoiding an impact between the cells and the container itself." The specification also discusses the criticality of selecting a proper collection fluid in order to reduce stress to the sperm cells.

The specification further teaches that the dilution process may effect the success rate of the insemination process. At page 21 of the specification, it is stated that "It has been discovered that dilution may create an effect upon the sperm cell's viability and so it may be appropriate to avoid too large a level of dilution by providing a smaller sample." However, the specification does not teach additional levels of dilution that can be used for insemination of bovine mammals.

With respect to claim 134, the step of staining the sperm cells is also known to be critical in influencing the viability of the sperm and effectiveness of the sorting procedure

to obtain viable sperm. Responsiveness to stain also varies depending on the type of stain. The specification (page 20) teaches that higher amounts of stain might "to some extent" provide better results. The specification teaches using a solution of 38uM Hoeschst 33342 stain. The specification does not specifically exemplify improved results using this concentration of stain. Claim 134 allows for the use of any stain, as long as it is present at a concentration of 38uM. However, the specification does not teach any stains other than Hoeschst 33342 that can be used at this concentration. In view of the unpredictability as to how a stain and the concentration of stain will effect the viability of sperm cells and the sorting process, undue experimentation would be required to practice the claimed invention using any stain at a concentration of 38uM.

Accordingly, the specification emphasizes the unpredictability in the art of using low dose sex-sorted sperm for AI and teaches that a multitude of factors interact in undefined ways to influence the viability of the sorted sperm and the success rate of insemination. However, the specification teaches only one particular set of conditions – i.e., the conditions set forth in Example 1 - that were shown to be effective for achieving success rates with low dose sex-sorted sperm comparable to success rates achieved using a typical high dosage, unsorted insemination sample. Yet, this examples does not utilize superovulated bovine. Given the unpredictability in the art of artificially inseminating superovulated bovine, the results obtained with single ovulating bovine cannot be extrapolated to superovulating bovine.

Amount of Direction or Guidance Provided by the Specification:

No specific guidance is provided in the specification as to how to practice a method of producing at least two embryos from a bovine mammal wherein the methods include superovulating the bovine mammal and inseminating the bovine mammal with one half of the typical unsorted sperm dosage to achieve success rates of at least 35%, 41%, 50%, or 90% up to 100% of that obtained with a typical unsorted insemination sample. Since there are no examples provided in the specification in which superovulated bovine are inseminated with one half of the typical unsorted sperm dosage or any other dosage of sperm, and there is no specific information provided as to how which of the critical process steps set forth in the specification may be omitted from the procedure and still obtain the stated levels of fertilization rates, insufficient guidance is provided to enable the skilled artisan to practice the claimed invention. The teachings in the specification regarding the combination of superovulation and insemination using low dosages of sperm are general in nature. The only guidance for practicing such a method includes a broad statement that superovulation may be combined with the high speed sorting and low dosage insemination techniques set forth in the specification (see page 22). Given the criticality of each of the process steps in preserving the integrity and activity of the sperm and in view of the high level of unpredictability associated with inseminating superovulated cows, additional guidance is required to enable the skilled artisan to practice the broadly claimed methods in which fertilization rates of at least 35%, 41%, 50%, or 90% up to 100% of a typical unsorted insemination sample are obtained.

Working Examples:

No working examples are provided in which multiple embryos from a bovine mammal are produced using a method comprising superovulating a female bovine mammal to produce at least two eggs, inserting a portion of an insemination sample having a number of sperm cells of at least half that of a typical unsorted insemination sample, and fertilizing the eggs at success rates of at least 35%, 41%, 50% or 90% of that of a typical unsorted insemination dosage.

Conclusions:

Case law has established that '(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" In re Wright 990 F.2d 1557, 1561. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that '(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the Court in Genetech Inc. v Novo Nordisk 42 USPQ2d 1001 held that '(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement".

In the instant case, for the reasons set forth above, the use of superovulatory bovine for artificial insemination purposes is highly unpredictable. Further, the use of low dosages of unsorted or sex sorted sperm is highly unpredictable. No specific guidance is provided in the specification as to how to practice a method in which

multiple embryos are produced from a bovine mammal which has been superovulated and which has been inseminated with a dosage that is at least half that of a typical unsorted insemination sample, and wherein fertilization of the eggs occurs at success rates of at least 35%, 41%, 50% or 90% of that of a typical unsorted insemination dosage. In view of the high level of unpredictability in the art and the lack of specific guidance provided in the specification, undue experimentation would be required to practice the invention as it is broadly claimed.

RESPONSE TO REMARKS

In the response filed September 13, 2006, Applicants state that "it appears the Office has not considered the Applicant's disclosure in the specification at page 22, lines 24-26 and page 23, lines 1-14. The specification at this location teaches embodiments specifically applicable to insemination of superovulated bovine. The Applicant believes the specification at this location discloses and enables all aspects recited in the claims."

Applicants remarks and the teachings set forth on page 22-23 of the specification have been fully considered but are not persuasive to overcome each of the present grounds of rejection.

Regarding the rejection set forth in paragraph 2 above (New Matter), the teachings on pages 22-23 of the specification do not provide support for the recitation in the claims of "fertilizing a plurality of said eggs at success levels selected from the group consisting of at least 35%, at least 41%, at least 50%, and at least 90% of a typical unsorted insemination dosage." In the example set forth on pages 22-23 of the

specification, it is stated that 12 heifers were superovulated and inseminated with sex-sorted sperm. The sperm used for insemination consisted of 184 ul of 3.36 x 10^6 sperm and "half the dose" was inseminated into each uterine horn. Embryos were recovered from 9 of the 12 heifers. There were 52 embryos at normal stages of development, 13 retarded embryos and 31 unfertilized ova. Based on this limited information, it is unclear as to what is intended to constitute the "success levels." If success levels are evaluated based on the fact that embryos were recovered from 9 of 12 heifers, then this would indicate a 75% fertilization success rate. However, this success rate is not stated in terms relative to "a typical unsorted insemination dosage" as is recited in the present claims. Further, a teaching of an absolute fertilization success rate of 75% does not provide basis for the recitation in the claims of "success levels selected from the group consisting of at least 35%, at least 41%, at least 50%, and at least 90%" - i.e. success levels of 35%, 36%...41%, 42%...50%, 51%...80%, 91%...99%...100% of a typical unsorted insemination dosage. Similarly, if success levels are determined based on the finding that 52 of 96 (54%) ova produced embryos at normal stages of development or that 65 of 96 (68%) ova were fertilized, these findings also do not provide basis for the recitation in the claims of "fertilizing a plurality of said eggs at success levels selected from the group consisting of at least 35%, at least 41%, at least 50%, and at least 90% of a typical unsorted insemination dosage."

Regarding the rejection set forth in paragraph 3 above (enablement), the claims are not limited to each of the embodiments disclosed in the example set forth on pages 22-23 of the specification. The response does not particularly discuss how this example

enables the claims as they are broadly written. As discussed above, the example set forth on pages 22-23 of the specification does not clearly describe a method in which fertilization success rates of at least 35% to 90%, and including 100%, relative to a typical unsorted insemination dosage, are achieved using a one half the number of a typical unsorted insemination dosage to inseminate superovulated bovine. Furthermore, it is unclear as to whether the dosage utilized in the example set forth on pages 22-23 constitutes "about one-half the number of sperm cells of a typical unsorted insemination dosage" as is required by the claims. Thereby, it is unclear as to whether the reported success rates were obtained using "about one-half the number of sperm cells of a typical unsorted insemination dosage." That is, the example states that sorted sperm were concentrated to 3.36×10^6 sperm/ml, 184 ul (6.18×10^5) were loaded in .25ml plastic straws, and "half the dose" was inseminated into each uterine horn. Accordingly, it appears that a total of 6.18×10^5 sperm were used for insemination. The specification (page 19) states that a typical unsorted sample consists of 1 to 10 million sperm. Relative to 1 million sperm, 6.18×10^5 sperm does not constitute "one-half the number of sperm cells of a typical unsorted insemination dosage." Additionally, as discussed in the above rejection, the fertilization success rate is effected by a number of criteria, including: the methodology used for superovulating the bovine; the use of frozen versus non-frozen sperm; the previous breeding history of the heifer; the side of insemination; the time at which sperm is used following sorting; the handling of sperm post sorting; the sampling rate at which sperm are sorted; apparatus used for sex sorting sperm; the sheath fluid used for the sorting process; the container used to collect sorted sperm;

and the effect of the staining procedure on sperm viability. For instance, the specification teaches that sperm cells are highly sensitive, that sperm from each type of organism may respond differently to different chemical environments (e.g., HEPES solution versus Citrate solution), that sorting, handling, and freezing processes damage sperm, and that it is extremely difficult to obtain sufficient quantities of sorted sperm that are not damaged and which can be used for successful artificial insemination procedures. Yet, the claims as a whole do not include each of these critical steps and limitations that are required to effectively use low dosages of sperm for artificial insemination. In the case of superovulated bovine, the use of low dosages of sperm is even further unpredictable. Applicants have previously argued that if one can anticipate how a change will effect the claimed invention, then there is predictability in the art. However, the specification has not taught how the extensive number of factors and parameters encompassed by the invention will effect the ability to use low dosages of sperm to inseminate superovulated bovine. Thereby, the effect of each of these parameters on fertilization success rates is unpredictable. Since the specification does not does not teach which of the critical parameters allow for the successful use of low dosage sperm samples to inseminate superovulated bovine, sufficient guidance is not provided in the specification as to how to practice the claimed method and achieve fertilization success levels of at least 35%, at least 41%, at least 50%, or at least 90% of a typical unsorted insemination dosage.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (571) 272-0747. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571)-272-0735.

The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866)-217-9197 (toll-free).

Carla Myers
Art Unit 1634

CARLA J. MYERS
PRIMARY EXAMINER